The Canadian Journal of Neurological Sciences (2024), 1–10
doi:10.1017/cjn.2024.283

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Original Article

Sex Differences in Moderate-to-Severe Traumatic Brain Injury Randomized Controlled Trials

Cecilia Flores-Sandoval[1], Heather M. MacKenzie[2,3], Emma A. Bateman[1,2,3], Keith Sequeira[2,3], Mark Bayley[4,5,6] and Robert Teasell[1,2,3]

[1]Parkwood Institute Research, Lawson Research Institute, London, ON, Canada, [2]Department of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, [3]St. Joseph's Health Care London, London, ON, Canada, [4]Division of Physical Medicine and Rehabilitation, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [5]KITE Research Institute, University Health Network, Toronto, ON, Canada and [6]Toronto Rehabilitation Institute, University Health Network, Toronto, ON, Canada

ABSTRACT: ***Background:*** Understanding sex differences among persons with moderate-to-severe traumatic brain injury (TBI) is critical to addressing the unique needs of both males and females from acute care through to rehabilitation. Epidemiological studies suggest that 7 of every 10 persons with moderate-to-severe TBI are male, with females representing about 30%–33%. ***Objective:*** To examine the proportion of female and male individuals included in randomized controlled trials (RCTs) of interventions for moderate-to-severe TBI. ***Methods:*** A systematic review was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines up to and including December 2022 using MEDLINE, PubMed, Scopus, CINAHL, EMBASE and PsycINFO databases. Studies were included if they met the following criteria: (1) human participants with a mean age ≥18 years, (2) ≥50% of the sample had moderate-to-severe TBI and (3) the study design was a RCT. Data extracted included author, year, country, sample size, number of female/male participants and time post-injury. ***Results:*** 595 RCTs met the criteria for inclusion, published between 1978 and 2022, totaling 86,662 participants. The average proportion of female participants was 23.14%, and the percentage increased a small but significant amount over time. There was a significantly lower percentage of female participants in RCTs initiated in the acute phase (≤ 1 month) when compared with RCTs conducted in the chronic phase (≥ 6 months) post-injury ($p < 0.001$). ***Conclusions:*** Female participants are underrepresented in RCTs of moderate-to-severe TBI. Addressing this underrepresentation is critical to establish effective treatments for all persons with TBI.

RÉSUMÉ : Différences entre les sexes dans les essais contrôlés randomisés portant sur des traumatismes craniocérébraux modérées à graves ***Contexte :*** Il est essentiel de comprendre les différences entre les sexes chez les individus victimes de traumatismes craniocérébraux (TCC) modérées à graves afin de répondre aux besoins uniques des hommes et des femmes, et ce, depuis les soins en phase aiguë jusqu'à la réadaptation. Les études épidémiologiques suggèrent par ailleurs que 7 individus sur 10 souffrant d'un TCC modéré ou grave sont des hommes, les femmes représentant environ 30 à 33 %. ***Objectif :*** Examiner la proportion de femmes et d'hommes inclus dans des essais contrôlés randomisés (ECR) portant sur des interventions pour des TCC modérés à graves. ***Méthodes :*** Jusqu'en décembre 2022 inclusivement, une étude systématique a été menée conformément aux lignes directrices de l'outil PRISMA en utilisant les bases de données MEDLINE, PubMed, Scopus, CINAHL, EMBASE et PsycINFO. Des études ont été incluses si elles répondaient aux critères suivants : (1) des participants humains avec un âge moyen ≥18 ans ; (2) ≥ 50 % de l'échantillon donnait à voir un TCC modéré à grave ; (3) la conception de l'étude était un ECR. Les données extraites comprenaient l'auteur, l'année, le pays, la taille de l'échantillon, le nombre de participants de sexe masculin ou féminin de même que le temps écoulé après le TCC. ***Résultats :*** Au total, 595 ECR ont répondu à nos critères d'inclusion. Ils ont été publiés entre 1978 et 2022 et incluaient 86 662 participants. La proportion moyenne de participants de sexe féminin était de 23,14 %, ce pourcentage ayant augmenté de façon faible mais significative au fil du temps. À noter que le pourcentage de participantes était significativement plus faible dans le cadre d'ECR lancés en phase aiguë (≤ 1 mois) que dans le cadre d'ECR menés en phase chronique (≥ 6 mois après le TCC ; $p < 0{,}001$). ***Conclusions :*** Les participants de sexe féminin demeurent sous-représentés dans le cadre d'ECR portant sur les TCC modérés à graves. Il est donc essentiel de remédier à cette sous-représentation afin de pouvoir établir des traitements efficaces pour tous les individus victimes d'un TCC.

Keywords: Female; randomized controlled trials; systematic review; sex; traumatic brain injury

(Received 18 December 2023; final revisions submitted 29 July 2024; date of acceptance 29 July 2024)

Corresponding author: Robert Teasell; Email: robert.teasell@sjhc.london.on.ca

Cite this article: Flores-Sandoval C, MacKenzie HM, Bateman EA, Sequeira K, Bayley M, and Teasell R. Sex Differences in Moderate-to-Severe Traumatic Brain Injury Randomized Controlled Trials. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2024.283

© The Author(s), 2024. Published by Cambridge University Press on behalf of Canadian Neurological Sciences Federation. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press

Highlights

- In 595 RCTs of moderate to severe TBI, the average proportion of females was 23.14%, with a small but significant increase over time.
- Fewer females were enrolled in RCTs conducted in the acute phase, compared of the chronic phase.
- The proportion of females was lower than expected by epidemiology alone.

Introduction

Broadly, traumatic brain injury (TBI) can be defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force."[1] TBI is a major global cause of disability and mortality and can have devastating consequences for affected individuals.[2] The severity of TBI can be categorized as mild, moderate or severe depending on neurological symptoms and indicators such as the duration of post-traumatic amnesia and loss of consciousness.[3] Injury severity is also commonly determined based on the initial Glasgow Coma Scale score, with lower scores indicating more severe injuries; individuals with TBI who present with scores of 13–15 are categorized as mild injuries, while individuals who present with scores ≤ 12 are categorized as moderate-to-severe injuries and often require specialized neurological and/or neurosurgical care.[2] According to the Public Health Agency of Canada,[4] even when categorized as being mild in severity, TBI can result in significant functional deficits.

Causes of TBI vary depending on population characteristics, such as geographical region, sex, age and other sociodemographic factors.[5] One important characteristic that influences the incidence, clinical presentation and outcomes post-TBI is sex, which is the focus of this review. Sex differences are apparent following TBI. Males are more likely to be hospitalized than females after moderate-to-severe TBI across all age groups[6] but are also more likely to leave the hospital against medical advice.[7] Epidemiological studies of TBI demonstrate that male patients are more likely to sustain and survive moderate-to-severe TBI than female patients; [8,9] studies suggest that 7 of every 10 persons with moderate-to-severe TBI are male, although one review found the ratio ranged from 1.2:1 to 4.6:1,[8–13] and a meta-analysis provided an estimate of males being 2.2 times as likely to sustain a TBI.[14] Together, these studies suggested that about 30%–33% of the population with TBI would be female, indicating a 2:1 male-to-female ratio. Male patients are more likely to experience TBI as a consequence of being struck by/against an object, whereas female patients are more likely to sustain their injuries from falls; males also experience a higher percentage of intentional injuries compared with females.[6,7] Females report higher symptom severities in the acute and subacute phases post-injury[7] and are more likely to seek medical and/or rehabilitation care after TBI than their male counterparts.[15] While females are more likely to die from a head injury than males, male sex has been shown to be an independent predictor of impaired executive function following TBI.[7]

Previous literature showed the underrepresentation of female individuals in clinical trials of various medical conditions.[16] For neurological diseases in particular, a previous systematic review showed that females were underrepresented in stroke trials, accounting for 38.8% of participants, and with lower female participation in studies conducted in the subacute and chronic phase post-stroke despite an almost equal incidence of stroke in males and females.[17] Given the importance of sex for patient outcomes post-TBI, understanding sex differences among research participants in RCTs is critical to address the needs of male and female individuals with moderate-to-severe TBI.

This review aimed to examine the proportion of female and male participants included in randomized controlled trials (RCTs) of interventions for moderate-to-severe TBI over time.

Method

Use of terminology

Sex and gender are variables that impact health, including prevention, diagnosis and therapeutic practices. The word "sex" refers to "the biological and physiological characteristics that distinguish males from females" and is a classification based on sexual organs and chromosomes.[18] In contrast, "gender" relates to socially constructed roles and behaviors within a cultural context.[19] While we acknowledge the importance of gender in TBI, this review focuses only on the participant's biological sex. We were unable to evaluate gender as it was not reported in any of the included studies.

Literature search

A systematic review of RCTs was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was conducted using MEDLINE, PubMed, Scopus, CINAHL, EMBASE and PsycINFO for all articles published up to and including December 2022. The search was restricted to RCTs published in the English language. Select key terms such as "brain injury," "head injury," "head trauma," "randomized," "placebo controlled" and "randomized controlled trial" were used in combination, and Medical Subject Headings (MeSH) was used as available in each database. Variations of these terms were used, as appropriate, for each separate database search. Full searches from each database were imported to EndNote version 8 (Camelot UK Bidco Limited [Clarivate]). All duplicate references were removed. First, titles and abstracts of unique articles were screened, and this was followed by a full-text review. Articles were assessed by two independent reviewers at the title and abstract screening stage and at the full-text stage, with a third reviewer assisting to solve cases of disagreement as needed. Two reviewers participated in the data extraction process.

Inclusion and exclusion criteria

Studies were included if they met the following a priori criteria: (1) human participants with a mean age ≥18 years, (2) ≥50% of the sample had moderate-to-severe TBI, (3) the study design was an RCT and (4) the study reported the sex of participants. Exclusion criteria were (1) >50% of the sample had mild TBI, (2) >50% of the sample had a brain injury of nontraumatic etiology, (3) protocols, (4) secondary analyses of RCTs and (5) studies with unclear injury etiology and/or severity. If the full-text version of an article could not be located, an email was sent to the corresponding author requesting a copy. Authors were given one month to respond before the article was excluded.

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press

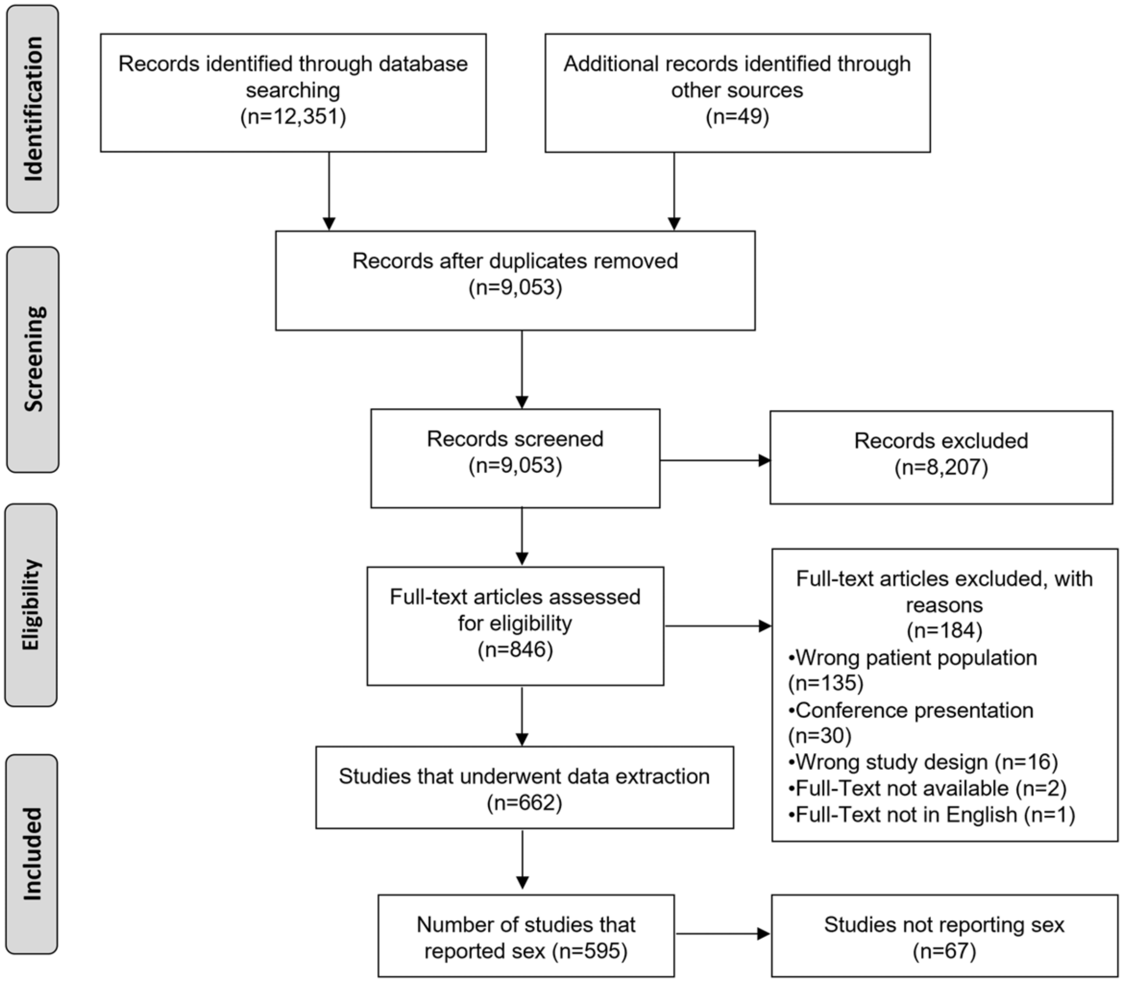

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Data extraction

Data extracted included author, year, country, sample size, number of female and male participants and time post-injury. If any data was missing, it was recorded as "Not Reported (NR)" for that particular variable.

Statistical analysis

Analyses were performed using IBM SPSS software (version 29.0.0). We performed a Levene's test for equality of variances. Accordingly, the Kruskal–Wallis test with post hoc analysis was performed to compare variables across different groups of RCTs with different characteristics. A binomial test was performed to examine sex differences by time post-injury, country and mean sample sizes.

Linear regression of the percentage of female participants and the year of publication was performed to show the trend of female participation over time. The regression analysis was done for RCTs after 1990 due to the small number of RCTs in previous years, affecting the homoscedasticity of data. Outliers were also identified in SPSS and removed from the data set for the aim of linear regression. A p-value of <0.05 was considered significant in all analyses.

Results

Study selection and data extraction

In total, 9,053 articles were screened for title and abstract; of these, 846 underwent full-text review. Finally, 662 RCTs were identified as RCTs of moderate-to-severe TBI; of these, 67 RCTs (10.1%) did not report the sex of the participants in the study, and 595 (89.9%) reported sex data for their participants. Therefore, 595 RCTs were included in the analysis (Figure 1).

Sex differences in RCTs over time

Collectively, the 595 RCTs reporting sex data enrolled 20,056 female and 66,606 male participants, resulting in a total of 86,662 participants for whom sex was reported. For those RCTs that reported the sex of their participants, the mean sample size and proportion of female participants are presented on a yearly basis from 1978 to 2022 in Table 1. This table also presents the number of studies per year that did not report sex data and the associated mean sample size. Table 1 and Figure 2 show that the annual proportion of female participants has increased over time, and the mean value from 1978 to 2022 was 23.14% (±13.6%).

Levene's test for equality of variances was found to be violated for the present analysis, for both female and male populations.

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press

Table 1. Proportion of female participants in randomized controlled trials (RCTs) of interventions for moderate-to-severe traumatic brain injury (TBI) presented by year

Year	Number of RCTs	Number of RCTs sex NR	% of NR	Number of females	Number of males	Total	Female %	Mean sample size	Mean sample size of NR
1978	1	0	0%	2	15	17	11.76%	17	
1979	2	1	50%	17	59	76	22.37%	50	3
1980	3	1	33%	26	104	130	20.00%	186	189
1981	2	1	50%	64	206	270	23.70%	185	100
1982	0	0							
1983	5	2	40%	113	509	622	18.17%	164.4	99.5
1984	3	2	67%	12	47	59	20.34%	73.7	81
1985	6	2	33%	9	94	103	8.74%	26.8	25.5
1986	3	0	0%	59	193	252	23.41%	85	
1987	2	1	50%	9	42	51	17.65%	77	96
1988	4	0	0%	22	106	128	17.19%	38.3	
1989	1	1	100%	0	0	0			40
1990	8	2	25%	340	522	862	39.44%	114.6	26.5
1991	8	1	13%	200	740	940	21.28%	145.6	39
1992	6	3	50%	102	426	528	19.32%	140.7	104.7
1993	11	2	18%	117	334	451	25.94%	69.4	75
1994	8	3	38%	204	729	933	21.86%	150.1	37
1995	8	2	25%	94	400	494	19.03%	79	35
1996	12	2	17%	169	660	829	20.39%	90.7	122.5
1997	10	1	10%	90	337	427	21.08%	47.7	15
1998	8	0	0%	337	1281	1618	20.83%	211.8	
1999	14	2	14%	173	716	889	19.46%	76	52.5
2000	12	1	8%	127	590	717	17.71%	61.8	14
2001	12	4	33%	167	302	469	35.61%	97.3	164.5
2002	9	1	11%	91	332	423	21.51%	67.4	152
2003	11	0	0%	189	533	722	26.18%	66.5	
2004	13	1	8%	2027	8468	10,495	19.31%	958.1	57
2005	14	2	14%	378	1008	1386	27.27%	107.1	19.5
2006	17	3	18%	428	1541	1969	21.74%	128.9	56
2007	14	0	0%	353	1163	1516	23.28%	108.5	
2008	21	1	5%	267	973	1240	21.53%	63.2	59
2009	27	0	0%	526	1260	1786	29.45%	74.8	
2010	15	1	7%	565	1823	2388	23.66%	164.6	23
2011	18	4	22%	313	1095	1408	22.23%	95.6	76.8
2012	26	3	12%	434	1424	1858	23.36%	79	16
2013	24	4	17%	219	1032	1251	17.51%	61.6	33.5
2014	27	1	4%	1010	2952	3962	25.49%	160.4	30
2015	20	4	20%	625	1625	2250	27.78%	140.3	123
2016	26	1	4%	438	1427	1865	23.49%	84.2	20
2017	37	0	0%	621	1715	2336	26.58%	67	
2018	33	1	3%	511	1940	2451	20.85%	78.3	119
2019	32	2	6%	2338	8931	11,269	20.75%	505.7	363
2020	39	0	0%	1021	2497	3518	29.02%	96.2	
2021	55	3	5%	4032	14,047	18,079	22.30%	340	82
2022	35	1	3%	1217	2408	3625	33.57%	104.8	50
Total	**662**	**67**	**10.12%**	**20,056**	**66,606**	**86,662**	**23.14%**	**151.7**	**78.9**

*NR = Not Reported.

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press

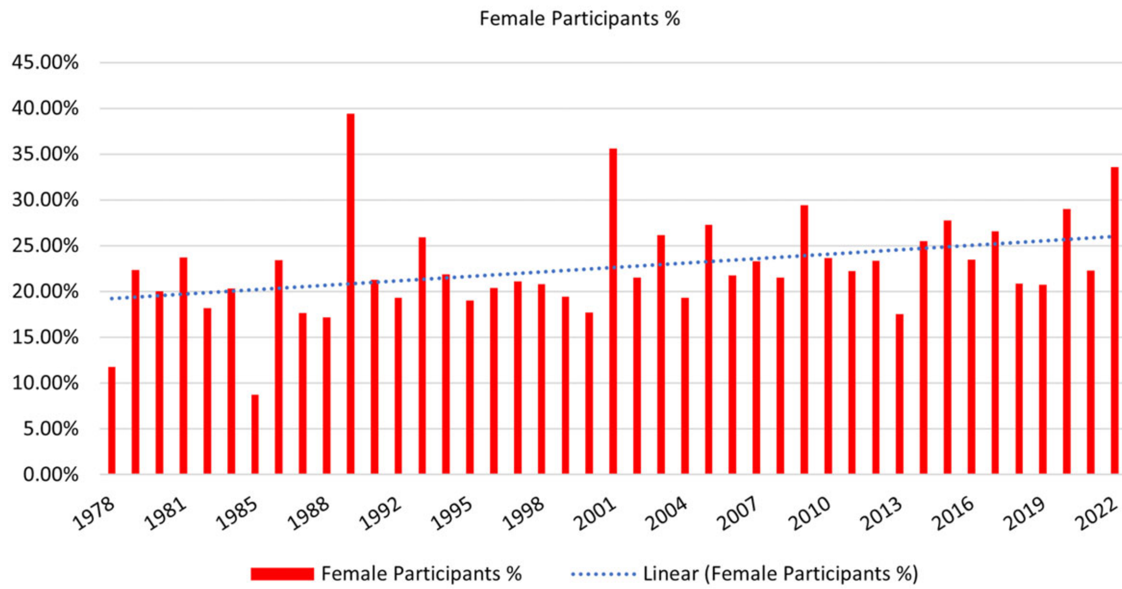

Figure 2. Bar graph depicting the proportion of female participants in randomized controlled trials (RCTs) of interventions for moderate-to-severe traumatic brain injury (TBI) presented by year. *No sex data were reported in the RCTs published in 1989; this year is not represented in the figure.

Consequently, a nonparametric test, the Kruskal–Wallis test, was performed. It found a significant difference between the number of male and female participants in TBI RCTs performed between 1978 and 2022 ($p < 0.001$); there were significantly more male than female participants.

Sample sizes and sex

Further analysis was conducted to compare the mean sample sizes of RCTs that reported sex data with those that did not. Levene's test for equality of variances was found to be violated for this analysis as well, both for studies reporting and not reporting sex data. Consequently, the Kruskal–Wallis test was performed. It found a significant difference between the mean sample sizes in TBI RCTs that reported sex data and those that did not between the years of 1978 and 2022 ($p < 0.001$). Sample sizes were significantly larger in those RCTs that did report sex data compared with those that did not.

Female participation over time

The percentage of female participants in RCTs was lower than male participants in the last five decades (Table 1). A linear regression analysis was performed to examine the trend in the percentage of female participants over time. The outliers were removed, and the analysis focused on data since 1990 as the data before that year were very limited, making the data heteroscedastic. The analysis showed a significant positive correlation between the proportion of female participants and time ($\beta = 0.188$, $t = 4.37$, $p < 0.001$), indicating a small increase in female enrollment over the last three decades (Figure 3).

Figure 4 presents the proportion of female participants over time after being divided into four groups (quartiles) containing roughly equal numbers of participants: 4760 female participants from 1978 to 2004 inclusive, 4493 female participants from 2005 to 2014 inclusive, 4533 female participants from 2015 to 2019 inclusive and 6270 female participants from 2020 to 2022 inclusive. There was relative stability in the proportion of female participants studied over time across quartiles, ranging from 21.15% to 24.86%.%. A binomial test was performed to compare the proportions of male and female participants for the RCTs conducted in each quartile time period. The difference in proportions between male and female participants was found to be significant for all four quartiles ($p < 0.001$); there were significantly more male than female participants.

Sex differences and time post-injury

We divided the RCTs according to time post-injury into acute, subacute and chronic phases (Table 3). Those RCTs categorized as acute studied participants ≤ 1 month post-injury. Those RCTs categorized as subacute studied participants from >1 month to <6 months post-injury, and those categorized as chronic included participants $\geq$6 months post-injury. Of the 595 RCTs that reported participant sex, the majority of RCTs ($n = 287$, 48.24%) studied participants in the acute phase post-TBI. Time post-injury was not reported in 124 RCTs (20.84%).

As reported in Table 2 and Figure 5, the proportion of females is higher in RCTs that enrolled participants in the chronic phase (29.76%), whereas the proportion of females is lowest in RCTs conducted during the acute phase post-injury (21.88%). A binomial test was performed to compare the proportion of male and female participants according to time post-injury, and this difference was found to be significant for all groups ($p < 0.001$); there were significantly more male than female participants in RCTs across all time points post-injury including the acute, subacute and chronic phases.

Sex differences and area of research focus

We divided RCTs into two groups according to the area of research focus: rehabilitation and medical/surgical management. RCTs were included in the rehabilitation category if they addressed the improvement of functional outcomes, including but not limited to cognition, motor function, emotional, behavioral and community

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press

Table 2. Proportion of female participants in moderate-to-severe traumatic brain injury (TBI) randomized controlled trials (RCTs) presented by time post-injury

Time post-injury	Number of RCTs	%	Number of females	Number of males	Total	Female %
Not reported (0)	124	20.84%	2489	6790	9279	26.82%
Acute (≤ 1 mo)	287	48.24%	14,931	53,318	68,249	21.88%
Subacute (>1 mo to <6 mo)	36	6.05%	686	1895	2581	26.58%
Chronic (≥ 6 mo)	148	24.87%	1950	4603	6553	29.76%
Total RCTs reporting sex	**595**		**20,056**	**66,606**	**86,662**	**23.14%**

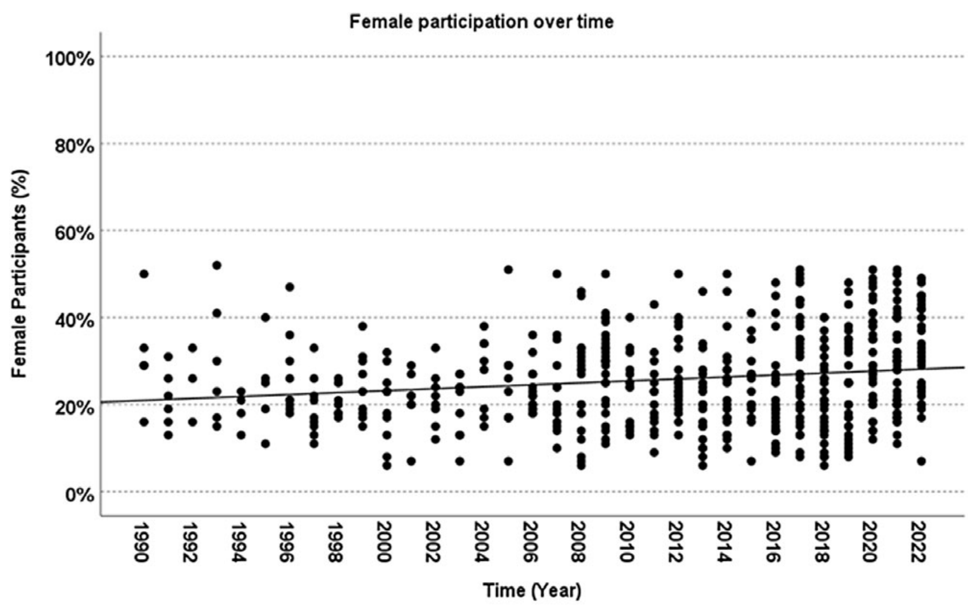

Figure 3. Linear regression of the proportion of female participants over time.

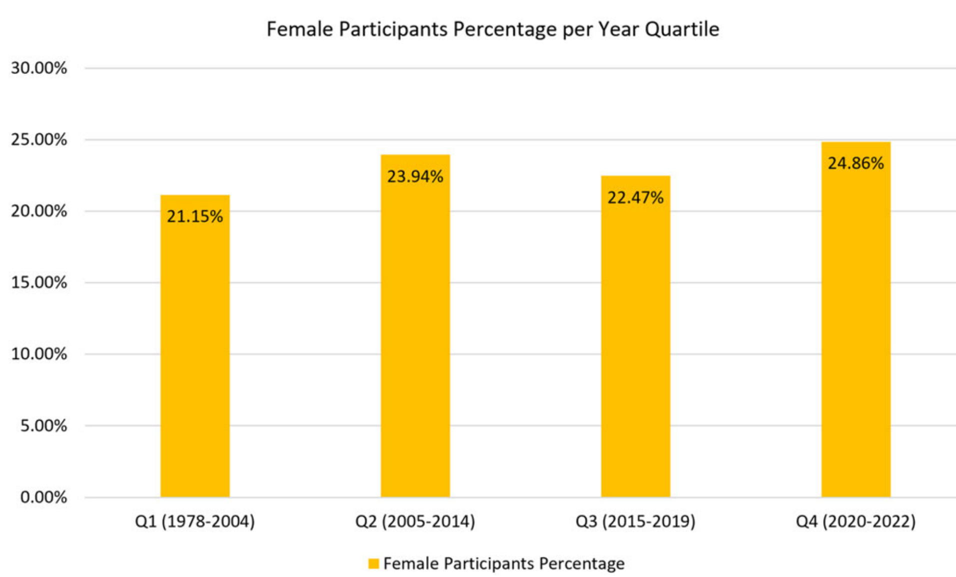

Figure 4. Bar graph depicting the proportion of female participants in moderate-to-severe traumatic brain injury (TBI) randomized controlled trials over time presented by quartiles.

participation. RCTs involving early rehabilitation occurring in critical care were also considered to belong to this group. RCTs were included in the medical/surgical management category if they addressed critical care and interventions to prevent mortality and further neurological damage, including but not limited to surgical interventions, pharmacological therapies, tracheostomy, red blood cell transfusion, temperature regulation management and intracranial pressure management and monitoring. RCTs in the

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press

Table 3. Proportion of female participants in moderate-to-severe traumatic brain injury (TBI) randomized controlled trials (RCTs) presented by area of research focus

Area of focus	Number of RCTs	%	Number of females	Number of males	Total	Female %
Medical/surgical	382	64.20%	16,807	58,323	75,130	22.37%
rehabilitation	213	35.80%	3249	8283	11,532	28.17%
Total RCTs reporting sex	**595**		**20,056**	**66,606**	**86,662**	**23.14%**

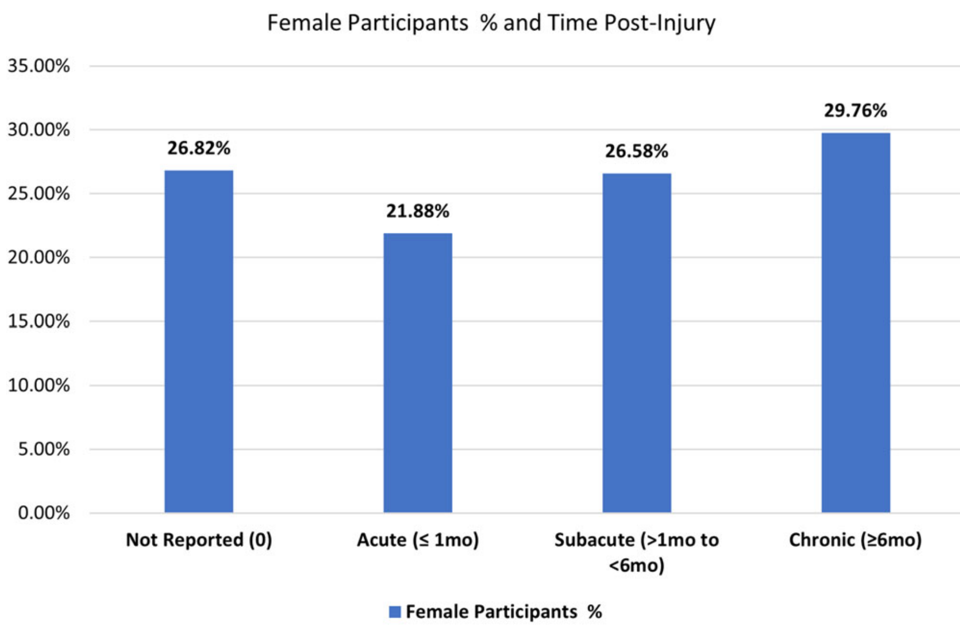

Figure 5. Bar graph depicting the proportion of female participants in moderate-to-severe traumatic brain injury (TBI) randomized controlled trials presented by time post-injury.

medical/surgical management group often addressed factors that occur almost exclusively in the acute phase post-injury; however, this was not a criterion for categorization.

Of the total 595 RCTs that reported participant sex, 382 (64.2%) belonged to the medical/surgical management group, while only 213 (35.8%) evaluated rehabilitation interventions. As reported in Table 3, there was a lower percentage of female participants in the medical/surgical group of RCTs (22.37%), when compared with the rehabilitation group (28.17%).

Discussion

Between 1978 and 2022, 662 RCTs were published on interventions for moderate-to-severe TBI. Of these, 595 (90%) reported data on the sex of the study participants, and 67 RCTs (10.1%) did not. Our analysis showed that, while there is a small but significant positive correlation between the proportion of female participants and time, females represent on average only 23.14% of RCT participants annually and this proportion has remained relatively consistent over time. Numerous studies indicate that 30%–33% of persons with moderate-to-severe TBI are female (2:1 male-to-female ratio); [10,11,14] however, the proportion of female participants in RCTs of persons with moderate-to-severe TBI is only 23.1%, or approximately a 3:1 male-to-female ratio. Based on the published incidence, female participants are underrepresented in TBI interventional RCTs.

Our observation that the enrollment of female participants in RCTs of interventions for moderate-to-severe TBI has seen only a minor upward shift over time requires further study. Underrepresentation of female participants in moderate-to-severe TBI RCTs is likely multifactorial including the lower incidence of TBI in females relative to males, recruitment strategies used for participants with moderate-to-severe TBI, differences in willingness to participate in clinical trials and a broader trend of underrepresentation of female participants in the medical research literature.[20]

There is a complex interplay between intrinsic factors, such as age, genetics and comorbid health conditions, and extrinsic factors, such as social and environmental determinants of health, which contribute to TBI risk and post-injury outcomes.[18] Biological sex is one such factor. A higher incidence of TBI has been reported in males, compared with females; a European systematic review reported that while the proportion of males was always greater than that of females, it ranged from 55% to 80%, depending on the country and year being examined.[21] Similarly, in the USA, the rate of TBI in males has been found to be nearly twice that of females.[22] This difference is particularly noticeable among young adult populations.[6] However, the higher proportion of males affected by TBI is not true for all ages. Among persons with TBI aged >75 years, the proportion of females affected has been shown to be greater than that of males.[23] It is likely that females' longer life expectancy is a major contributing reason for this finding; however, further research exploring this epidemiological phenomenon and more research on females aging with TBI are still needed to examine research trends and long-term health outcomes in this population.[24,25]

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press

Male individuals are more likely to be hospitalized for a TBI than females, which suggests that male individuals are at a higher risk of sustaining more severe injuries that require hospitalization.[26] Concurrently, rates of fatal TBI have been found to be significantly higher among males compared with females.[22] Males are also more likely to work in high-risk occupations, such as in the construction industry or the military, and are particularly vulnerable to TBI as a result of these exposures; [27] in a study conducted in Ontario, Canada, males were five times more likely to sustain a TBI in the workplace than females.[7] As male patients are more likely to experience moderate-to-severe TBI, this may explain the predominance of male participants in moderate-to-severe TBI RCTs. However, female representation in these studies remains lower than expected by epidemiology alone.

Discrepancies in enrollment in RCTs by sex have also been observed by other authors across multiple fields of study other than moderate-to-severe TBI.[28] Female sex-related factors, such as the potential for pregnancy and breastfeeding, have long been recognized as contributors to the exclusion of female research participants from clinical trials and remain inadequately addressed.[15] Numerous studies have shown that female participants continue to be underrepresented in RCTs from other disease groups. For instance, in a systematic review of medicine RCTs published in 2017, Daitch *et al.* found that the enrollment rate for female participants was 41% across all studies.[20] In an analysis of RCTs conducted in the USA, those focused on neurological conditions had some of the lowest rates of female participant representation, with a median female enrollment of 46.7% in US government-funded clinical trials.[28] The underrepresentation of female participants in studies of neurological conditions is also evident in two systematic reviews of RCTs in the stroke population, which reported that the proportion of female participants was 37.4%–38%.[19,30] Although these reviews found relatively low rates of female participant enrollment, their male-to-female ratios remain much higher than those in RCTs involving individuals with moderate-to-severe TBI.

TBIs sustained as a result of intimate partner violence (IPV) are often underreported and disproportionally affect females;[31–33] persons injured through IPV may not necessarily have the same access to medical care or maybe more reticent to seek medical assistance than persons with other mechanisms of injury.[31,33] For female individuals who sought medical care for a fracture resulting from IPV, the probability of concurrent TBI was 0.77, suggesting that female individuals may not seek care for IPV-related TBI specifically.[33] Taken together, these findings and those of this review suggest that addressing the underrepresentation of female participants in TBI RCTs may require novel recruitment strategies.

Many moderate to severe TBI studies rely on recruiting hospitalized inpatients.[34] Because male individuals are more likely to be hospitalized with TBI, this may confer a greater opportunity to males for participation in RCTs. Another possibility is that male individuals may be more willing to participate in research. Although the authors are not aware of evidence of sex differences in volunteer bias for moderate-to-severe TBI, sex is a significant factor in research participation in numerous other areas.[35,36] Alternatively, there may also be lingering social barriers that favor the recruitment of males over females.[29] Other potential reasons for female underrepresentation may be related to cultural factors that discourage or prevent female individuals from participating in trials without the permission from a spouse or male family member.[37]

In our study, the proportion of female participants in moderate-to-severe TBI RCTs did improve significantly over time, but the increase was nevertheless small, even while considering the epidemiology of moderate-to-severe TBI. More equal representation of females and males is critical to ensure the generalizability of research findings and to determine the safety and effectiveness of treatments for the female population.[15] The greater representation of female participants in RCTs taking place in the chronic phase when compared with the acute phase is intriguing, given that the vast majority of acute phase RCTs are medical/surgical interventions and the great majority of chronic phase RCTs are rehabilitation interventions. This requires further study but may be related to the nature of the intervention, the time when it is delivered or a greater proportion of females entering rehabilitation. At a minimum, the authors urge that research in moderate-to-severe TBI include reporting on demographic data such as sex to further our understanding of the generalizability of results to future patients with TBI, whether male or female.

Limitations

While we acknowledge the impact of gender and intersecting sexual identities, for this review, we considered only biological sex. We were unable to evaluate gender as it was not reported in any of the included studies. Furthermore, our study only considered RCTs of moderate-to-severe TBI so the findings may not be generalizable across the full spectrum of injury severity. We also excluded studies that did not report injury severity, injury etiology or the proportion of participants affected by traumatic versus nontraumatic etiologies.

Conclusion

Of 662 moderate-to-severe TBI RCTs, 595 (90%) reported sex data and represented 86,662 participants. Overall, the average annual proportion of female participants in these studies was 23.14%, and it remained generally stable over time with a small but significant increase in female recruitment. There was a significantly lower proportion of females recruited in RCTs initiated in the acute phase post-injury when compared with RCTs conducted in the chronic phase. The fact that the proportion of female recruitment into TBI RCTs has not changed much over the course of five decades is difficult to explain, and further research investigating the factors at play is needed. The low proportion of female participants limits the generalizability of the existing body of literature as well as our understanding of how best to meet the needs of females who have sustained a moderate-to-severe TBI.

Acknowledgments. The authors would like to acknowledge the valuable contributions of Muskan Sait and Sarvenaz Mehrabi to the preparation of this manuscript.

Author contributions. CFS conducted searches, extracted, analyzed and managed the data and contributed to manuscript writing. HMM contributed to manuscript writing and editing. EAB contributed to manuscript writing and editing. KS contributed to manuscript writing and editing. MB provided overall supervision and contributed to editing and writing. RT conceptualized and led the project, supervised data analysis and extraction and contributed to writing.

Funding statement. Funding was provided by the Ontario Ministry of Health and Long-Term Care through Neurotrauma Pathways and the St Joseph's Health Care (London) Foundation.

Competing interests. *Dr Robert Teasell* received support from the Ontario Ministry of Health and Long-Term Care for this project; in the past 36 months,

he received grants/support from the Heart and Stroke Foundation of Ontario; he also received payment for expert testimony (Medlegal work for local attorneys) and participated on a safety monitoring board for the DOSE study (osteoporosis drug in Spinal Cord Injury); in the last three years, he received a grant from Abbvie (makers of Botox) for stroke research. *Dr Heather M. MacKenzie:* Within the past 36 months, she received support from the Academic Medical Organization of Southwestern Ontario, Opportunities Fund (personal payment); Lawson Health Research Institute, Internal Research Fund; Ontario Brain Institute, Craig H. Neilsen Foundation; Ministry of Health of Ontario; and Ontario Neurotrauma Foundation (payments made to institution). *Dr Mark Bayley* received support from the UHN Foundation (not profit); in the past 36 months, he received grants from the Canadian Institutes of Health Research, Brain Canada Foundation, Ministry of Health Ontario Research Branch, Heart and Stroke Foundation Canada, National Institutes of Health (USA) and National Health and Medical Research Council Australia; he also held a leadership role as chair in Rehabilitation Care Alliance of Ontario (unpaid) and as co-chair of the March of Dimes After Stroke Advisory Committee (unpaid); he received a stipend for leadership role as Medical Director of UHN – Toronto Rehabilitation Institute. *Dr Keith Sequeira*: No conflict of interest to disclose. *Dr Emma A. Bateman:* No conflict of interest to disclose. *Cecilia Flores-Sandoval*: No conflict of interest to disclose. An abstract of the present research had been previously submitted to the World Federation for Neurorehabilitation's 13th World Congress Conference.

Transparency statement. A protocol was not registered on the International Prospective Register of Systematic Reviews previous to this submission. An initial search was conducted up to June 2021, with an updated search conducted up to and including December 2022. We did not perform Grading of Recommendations Assessment, Development and Evaluation (GRADE) or Cochrane risk of bias.

References

1. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil*. 2010;91:1637–40. DOI: 10.1016/j.apmr.2010.05.017.
2. Robinson CP. Moderate and severe traumatic brain injury. *Continuum (Minneap Minn)*. 2021;27:1278–300. DOI: 10.1212/con.0000000000001036.
3. Blennow K, Brody DL, Kochanek PM, et al. Traumatic brain injuries. *Nat Rev Dis Primers*. 2016;2:16084. DOI: 10.1038/nrdp.2016.84.
4. Public Health Agency of Canada. *Spotlight on Traumatic Brain Injuries Across the Life Course*. Government of Canada. 2020.
5. Haarbauer-Krupa J, Pugh MJ, Prager EM, Harmon N, Wolfe J, Yaffe K. Epidemiology of chronic effects of traumatic brain injury. *J Neurotrauma*. 2021;38:3235–47. DOI: 10.1089/neu.2021.0062.
6. Colantonio A, Saverino C, Zagorski B, et al. Hospitalizations and emergency department visits for TBI in Ontario. *Can J Neurol Sci*. 2010;37:783–90. DOI: 10.1017/s0317167100051441.
7. Mollayeva T, Mollayeva S, Colantonio A. Traumatic brain injury: sex, gender and intersecting vulnerabilities. *Nat Rev Neurol*. 2018;14:711–22. DOI: 10.1038/s41582-018-0091-y.
8. Andriessen TM, Horn J, Franschman G, et al. Epidemiology, severity classification, and outcome of moderate and severe traumatic brain injury: a prospective multicenter study. *J Neurotrauma*. 2011;28:2019–31. DOI: 10.1089/neu.2011.2034.
9. Watanitanon A, Lyons VH, Lele AV, et al. Clinical epidemiology of adults with moderate traumatic brain injury. *Crit Care Med*. 2018;46:781–2991. DOI: 10.1097/CCM.0000000000002991.
10. Langlois JA, Kegler SR, Butler JA, et al. Traumatic brain injury-related hospital discharges: results from a 14-state surveillance system, 1997. *MMWR Surveill Summ*. 2003;52:1–20.
11. Nguyen R, Fiest KM, McChesney J, et al. The international incidence of traumatic brain injury: a systematic review and meta-analysis. *Can J Neurol Sci*. 2016;43:774–85.
12. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir (Wien)*. 2015;157:1683–96. DOI: 10.1007/s00701-015-2512-7.
13. Ratcliff JJ, Greenspan AI, Goldstein FC, et al. Gender and traumatic brain injury: do the sexes fare differently? *Brain Inj*. 2007;21:1023–30. DOI: 10.1080/02699050701633072.
14. Frost RB, Farrer TJ, Primosch M, Hedges DW. *Prevalence of Traumatic Brain Injury in the General Adult Population: A Meta-analysis*. S. Karger AG Basel; 2013: 154–9.
15. Yakerson A. Women in clinical trials: a review of policy development and health equity in the Canadian context. *Int J Equity Health*. 2019;18:56. DOI: 10.1186/s12939-019-0954-x.
16. Feldman S, Ammar W, Lo K, Trepman E, van Zuylen M, Etzioni O. Quantifying sex bias in clinical studies at scale with automated data extraction. *JAMA Netw Open*. 2019;2:e196700–e.
17. Mehrabi S, Harnett A, Saikaley M, et al. Female enrollment in rehabilitation trials: a systematic review of reporting sex, and female participation in randomized controlled trials of post-stroke upper extremity rehabilitation Over 50 Years. *Arch Phys Med Rehab*. 2024;105:1399–1406.
18. Giordano KR, Rojas-Valencia LM, Bhargava V, Lifshitz J. Beyond binary: influence of sex and gender on outcome after traumatic brain injury. *J Neurotrauma*. 2020;37:2454–9. DOI: 10.1089/neu.2020.7230.
19. Ristvedt SL. The evolution of gender. *JAMA Psych*. 2014;71:13–4. DOI: 10.1001/jamapsychiatry.2013.3199.
20. Daitch V, Turjeman A, Poran I, et al. Underrepresentation of women in randomized controlled trials: a systematic review and meta-analysis. *Trials*. 2022;23:1038–. DOI: 10.1186/s13063-022-07004-2.
21. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of traumatic brain injury in Europe: a living systematic review. *J Neurotrauma*. 2021;38:1411–40. DOI: 10.1089/neu.2015.4126.
22. Corrigan JD, Selassie AW, Orman JAL. The epidemiology of traumatic brain injury. *J Head Trauma Rehabil*. 2010;25:72–80. DOI: 10.1097/HTR.0b013e3181ccc8b4.
23. Mauritz W, Brazinova A, Majdan M, Leitgeb J. Epidemiology of traumatic brain injury in Austria. *Wien Klin Wochenschr*. 2014;126:42. DOI: 10.1007/s00508-013-0456-6.
24. Harris JE, Colantonio A, Bushnik T, et al. Advancing the health and quality-of-life of girls and women after traumatic brain injury: workshop summary and recommendations. *Brain Inj*. 2012;26:177–82.
25. Valera EM, Joseph A-LC, Snedaker K, et al. Understanding traumatic brain injury in females: a state-of-the-art summary and future directions. *J Head Trauma Rehabil*. 2021;36:E1–E17.
26. Mollayeva T, Colantonio A. Gender, sex and traumatic brain injury: transformative science to optimize patient outcomes. *Healthc Q*. 2017;20:6–9. DOI: 10.12927/hcq.2017.25144.
27. Colantonio A, McVittie D, Lewko J, Yin J. Traumatic brain injuries in the construction industry. *Brain Inj*. 2009;23:873–8. DOI: 10.1080/02699050903036033.
28. Steinberg JR, Turner BE, Weeks BT, et al. Analysis of female enrollment and participant sex by burden of disease in US clinical trials Between 2000 and 2020. *JAMA Netw Open*. 2021;4:e2113749–e. DOI: 10.1001/jamanetworkopen.2021.13749.
29. Carcel C, Harris K, Peters SA, et al. Representation of women in stroke clinical trials: a review of 281 trials involving more than 500,000 participants. *Neurology*. 2021;97:e1768–e74. DOI: 10.1212/WNL.0000000000012767.
30. Melloni C, Berger JS, Wang TY, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circ Cardiovasc Qual Outcomes*. 2010;3:135–42. DOI: 10.1161/CIRCOUTCOMES.110.868307.
31. Colantonio A. Sex, gender, and traumatic brain injury: a commentary. *Arch Phys Med Rehabil*. 2016;97:S1–4. DOI: 10.1016/j.apmr.2015.12.002.
32. Raskin SA, DeJoie O, Edwards C, et al. Traumatic brain injury screening and neuropsychological functioning in women who experience intimate partner violence. *Clin Neuropsychol*. 2023;38:1–23. DOI: 10.1080/13854046.2023.

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press

33. Turkstra LS, Salanki K, MacIntyre E, et al. What is the prevalence of intimate partner violence and traumatic brain injury in fracture clinic patients? *Clin Orthop Relat Res*. 2023;481:10–1097. DOI: 10.1097/CORR,0000000000002329.
34. Peterson AB, Xu L, Daugherty J, Breiding MJ. *Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths, United States, 2014*. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. 2019.
35. Ganguli M, Lytle ME, Reynolds MD, Dodge HH. Random versus volunteer selection for a community-based study. *TJ Gerontol A Biol Sci Med Sci*. 1998;53:M39–M46. DOI: 10.1093/gerona/53a.1.m39.
36. Robinson K, Dayer K, Mirichlis S, Hasking P, Wilson M. Who are we missing? Self-selection bias in nonsuicidal self-injury research. *Suicide Life Threat Behav*. 2023;53:843–52. DOI: 10.1111/sltb.12987.
37. Persampieri L. Gender and informed consent in clinical research: beyond ethical challenges. *BioLaw Journal-Rivista di Biodiritto*. 2019; 1S:65–87.

https://doi.org/10.1017/cjn.2024.283 Published online by Cambridge University Press